

## **REMARKS**

Claims 4-6 were identified in the Office Action as pending. Claims 1-3 and 7-29 have been cancelled without prejudice to the filing of continuing applications. Claims 4-6 have been amended. No new matter is added by these amendments. New claims 30-35 are presented. Support for new claims 30-31 and 33-34 can be found, for example, in the specification at pages 32, line 20 and in Examples 3 and 4, and support for new claims 33 and 35 can be found, for example, at page 49, lines 11-12. The rejections set forth in the Office Action mailed July 11, 2005, are traversed in part by amendment and in part by argument as set forth herein.

### **1. Rejections under 35 USC §102**

#### **Jia et al.**

Claim 4 stands rejected under 35 U.S.C. §102(b) as being anticipated by Jia *et al.* The Patent Office specifically alleges that Jia *et al.* teaches the identical active method step of the claimed invention. Jia *et al.* teaches the addition of NO to oxyHb, but the result of said experiment is said by Jia *et al.* to have produced metHb (see legend for Figure 1B on page 222 of Jia *et al.*). The results obtained by Jia *et al.*, therefore, are different from the claimed invention. As discussed in the instant specification (see for example page 16, lines 3-12 of the specification) metHb is formed when NO interacts with oxyHb under conditions that favor the normal tight (T) structure of hemoglobin, as demonstrated experimentally in buffers comprising high phosphate concentrations, while SNO-Hb is formed under conditions where the relaxed (R) structure is favored (see for example page 22, lines 8-19).

Applicants have amended Claim 4 to more particularly point out that the method of producing S-nitrosohemoglobin comprises the addition of NO to oxyHb under conditions sufficient to maintain the relaxed (R) structure of hemoglobin. Support for this amendment is found in the specification, for example, on page 23, lines 9-11, and Examples 2-4, which demonstrate that metHb is formed at high phosphate concentrations

(which favor the tight (T) structure of hemoglobin) and S-nitrosohemoglobin is produced at low phosphate concentrations (which favor the R structure of hemoglobin).

As pointed out above, the formation of metHb occurs when NO is added to oxyHb under conditions that disfavor the R structure of hemoglobins, such as in conditions having high concentrations of phosphate (*i.e.* 100 mM phosphate). See, for example, Figures 1A-1D and Figures 3A-3D of the instant specification and Examples 2 and 3 on page 46 of the specification. Jia *et al.* says nothing about producing S-nitrosohemoglobin using NO and oxyHb. Consequently, the Jia *et al.* reference does not teach production of S-nitrosohemoglobin by adding NO to oxyHb under conditions sufficient to maintain the R structure of hemoglobin.

As a general rule, for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. Corning Glass Works v. Sumitomo Electric, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. Connell v. Sears, Roebuck & Co., 220 U.S.P.Q 193, 1098 (Fed. Cir. 1983). Therefore, since Jia *et al.* does not teach a method of producing S-nitrosohemoglobin comprising adding free NO to oxyHb under conditions sufficient to maintain the R structure of hemoglobin, Jia *et al.* cannot anticipate Claim 4. Therefore, Applicants respectfully request that this ground of rejection be reconsidered and withdrawn.

#### Yonetani et al.

Claims 5 and 6 stand rejected under 35 U.S.C. §102(e) as being anticipated by Yonetani *et al.* (US Patent No. 6,087,087). Yonetani *et al.* teaches methods for producing  $\alpha$ -nitrosyl hemoglobin in erythrocytes. The Office alleges that Yonetani *et al.* teaches the identical active step as the methods of the claimed invention. However, Yonetani *et al.* at column 16, lines 7-9, teaches that NO in the blood diffuses into erythrocytes and reacts with oxyHb to form metHb, not S-nitrosohemoglobin. Thus, Yonetani *et al.* does not teach that NO added to oxyHb will produce intraerythrocytic S-nitrosohemoglobin.

Claim 5 has been amended to include that NO is added to erythrocytes under conditions sufficient to maintain the R structure of hemoglobin (support for this amendment is described above and also is found on page 32, lines 15-20 of the specification). Since, as pointed out above, a prior art reference must teach every element of a claim to anticipate that claim, Yonetani *et al.* cannot anticipate Claim 5, because Yonetani *et al.* does not teach adding NO to oxyHb under conditions sufficient to maintain the R structure of hemoglobin to produce S-nitrosohemoglobin. Therefore, Applicants respectfully request that this ground of rejection be reconsidered and withdrawn.

The Patent Office asserts that Claims 5 and 6 are drawn to methods for producing S-nitrosohemoglobin. Applicants wish to clarify that Claim 6 is broadly drawn to a method of producing a composition comprising intraerythrocytic NO at greater than about 50 nM, which is not necessarily a method for producing S-nitrosohemoglobin. Yonetani *et al.* do not teach or suggest producing a composition comprising intraerythrocytic NO at greater than about 50 nM. Therefore, since Yonetani *et al.* do not teach every element of Claim 6 (*i.e.* producing a composition comprising intraerythrocytic NO at greater than about 50nM), Yonetani *et al.* cannot anticipate Claim 6. Consequently, Applicants respectfully request that this ground of rejection be reconsidered and withdrawn.

## **2. Rejections under 35 USC §112**

### **Incomplete claims**

Claims 4-6 stand rejected under 35 USC §112 second paragraph as being incomplete for omitting essential steps. The Patent Office alleges that the missing steps are the conditions necessary to achieve S-nitrosohemoglobin. As pointed out above, Claim 6 is not specifically drawn to a method of producing S-nitrosohemoglobin. However, Claim 6 has been amended to more particularly point out that the amount of free NO added to the composition is sufficient to yield intraerythrocytic NO concentration of greater than about 50nM. Therefore, Applicants submit that Claim 6 satisfies the requirements of 35 USC §112, and is not incomplete.

As pointed out above, Claims 4 and 5 have been amended to recite that an amount of NO that is sufficient to produce S-nitrosohemoglobin is added to oxyHb under conditions sufficient to maintain the R structure of hemoglobin and wherein the free NO is added in an amount sufficient to produce S-nitrosohemoglobin. As discussed above, the addition of NO to oxyHb will predominantly form metHb under conditions that favor the T structure of hemoglobin, and will form S-nitrosohemoglobin under conditions that favor the R structure of hemoglobin. Therefore, Applicants contend that the claims as presently amended are complete. Consequently, Applicants respectfully request that this ground of rejection be reconsidered and withdrawn.

#### Enablement

Claims 4-6 stand rejected under 35 USC §112 second paragraph as failing the enablement requirement. Specifically, the Patent Office alleges that the specification fails to teach conditions necessary to achieve the claimed product of S-nitrosohemoglobin. However, as pointed out above, the specification does teach the conditions under which NO and oxyHb can form S-nitrosohemoglobin. For example, on page 22, lines 13-16, the specification teaches that S-nitrosohemoglobin formation requires conditions that maximize vacancies of molecules in R structure while minimizing molecules in the T structure. As discussed on page 16, lines 4-7, of the specification, an example of conditions that disfavor the R structure include high phosphate concentrations. In addition, Example 4 describes the production of S-nitrosohemoglobin by the addition of NO to oxyHb in a buffer comprising a low concentration of phosphate, which maintains the R structure (see Figures 4C and 4D). Consequently, Applicants respectfully contend that the specification does enable claims 4-6 by providing conditions under which NO and oxyHb will react to produce S-nitrosohemoglobin. Therefore, Applicants submit that the claims do not fail the enablement requirement, and respectfully request that this ground of rejection be reconsidered and withdrawn.

### CONCLUSION

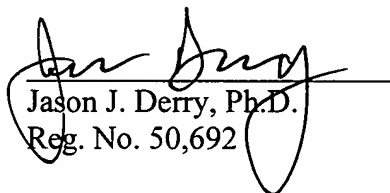
Applicants submit that the application satisfies the statutory requirements of Title 35 of the United States Code. Allowance of the claims is thereby respectfully solicited.

The Examiner is invited to contact the undersigned representative by telephone at (312) 913-0001 if a discussion is believed to be helpful.

Respectfully submitted,

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